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(54) Title: MELT GRANULATION

(57) Abstract

The present invention discloses a simple one–step process of coating by means of melt granulation for effective masking of bitterness, and a new, patient–friendly oral pharmaceutical formulation suitable also for diabetics, which at the same time also enables variations in the rate and site of the release of the active component.

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MELT GRANULATION

Technical Field

International Patent Classification: A 61 J 3/02, C 07 G 11/00

The present invention belongs to the field of pharmaceutical technology and discloses melt granulation.

More specifically, the present invention discloses a simple one-step process for coating clarithromycin or derivatives thereof by means of melt granulation in order to effectively cover their bitterness, as well as a new, patient-friendly oral pharmaceutical formulation suitable also for diabetics, which at the same time also enables variations in the rate and site of the release of the active component.

Technical Problem

Clarithromycin is a slightly basic, practically water-insoluble, acid-sensitive macrolide antibiotic with a very bitter taste that remains in the mouth for several hours after taking a therapeutical dose.

Since some groups of patients (children, the elderly, patients with swallowing disorders) cannot take solid medical preparations (tablets, capsules) and the same groups are also very sensitive to the (un)acceptable taste of a medical preparation, there existed a need to find an effective technological solution to cover or mask the bitter taste of clarithromycin or its derivatives, i.e. a need to prepare a suspension for oral use, which will be both patient-friendly and therapeutically effective.

The commercially available oral suspension with clarithromycin contains a considerable amount of sugar (which does not eliminate the bitter aftertaste), but it

still has a relatively unpleasant taste. Moreover, the technology of the preparation thereof is a multistep one and hence expensive.

Thus, the present invention arises from the need to prepare an oral suspension with clarithromycin or derivatives thereof, which will be tasty, effective and obtainable by means of a one-step process.

Prior Art

Clarithromycin is a semi-synthetic antibiotic obtained by methylation of erythromycin in the lactone position C6. The synthesis is described in US 4,331,803 and US 4,672,109. It is active against gram-positive bacteria and, due to the broad spectrum of antimicrobial activity, it is used clinically. On the market it is available in the form of coated tablets, suspensions and prolonged-release tablets.

Different oral pharmaceutical formulations with clarithromycin are also described in the following patents:

JP 85/163823 discloses an oral medicament with clarithromycin, citric acid increasing the absorption of antibiotic in the alimentary tract, disintegrants, excipients and lubricants.

EP 0277042 discloses an oral pharmaceutical formulation (also with macrolides) with an improved taste and having a coating of particular polymers (especially polyvinyl acetal diethylaminoacetate - AEA), soluble in gastric juice and with a mean particle diameter under 60 μm.

US 4,808,411 discloses a pharmaceutical formulation with erythromycin or its derivatives and a carbomer, possibly in the form of ion-complex particles coated with a polymer, which can be suspended in a liquid carrier.

JP 01-308,223 discloses the preparation of film-coated microgranules of a sustained-release medicament containing AEA and water in addition to clarithromycin.

EP 0302370 and WO 90/08537 disclose improved oral pharmaceutical formulations (oil solution, suspension, emulsion) of erythromycin and derivatives to be filled into soft gelatine capsules with N-methyl-pyrrolidone.

EP-B-0420992 discloses a process for the production of an oral pharmaceutical formulation (also with macrolides) with a masked taste, which comprises spraying a medicament suspension into a cold water solution of AEA.

JP 02-279,622 discloses oral medicaments with AEA, prepared by a fine granulation of a medicament (clarithromycin) dispersed in a melted oil base (cacao butter), followed by suspending the fine particles in a water solution of AEA and spray-drying the suspension.

US 5,017,383 discloses a method for the production of a finely coated pharmaceutical formulation, which comprises mixing frozen particles of a liquid medium with a medicament (also with macrolides) and a coating in the form of a fine powder adhering onto the surface of the particles.

JP 05-255,075 discloses melt granulation of macrolides, wherein the coating consists of polymers soluble in stomach (particularly Eudragit E), which are dispersed in compounds with a low melting point. The final granulation is performed by spraying. The final preparation of a dry syrup is accomplished by mixing granules with sugar and hydroxypropyl methyl cellulose (HPMC).

US 5,599,556 and US 5,609,909 disclose the masking of the taste of encapsulated clarithromycin particles with prolamine coatings prior to the preparation of a suspension.

WO 96/34628 discloses an oral pharmaceutical formulation (also with macrolides) for masking the taste (particularly a dry syrup), which contains a medicament with an unpleasant taste, a higher polymer soluble in stomach (particularly AEA and Eudragit E) and a monoglyceride with a low melting point (particularly glyceryl monostearate) in the stable crystal form β (transformed from the metastable form α by additional shaking at increased temperature), and a method of masking the taste.

WO 97/16174 discloses a process of water granulation of a macrolide antibiotic with a carbomer (acrylic polymer).

US 5,705,190 discloses a controlled-release solid oral pharmaceutical formulation (also of clarithromycin) containing a medicament weakly soluble in water, a water-soluble alginate salt, a complex salt of alginic acid with a metal cation and an organic carboxylic acid facilitating the dissolution of the medicament.

US 5,707,646 discloses a pharmaceutical formulation (also with macrolides) for oral use (particularly a dry syrup) containing a medicament with an unpleasant taste, a functional polymer (particularly AEA or/and Eudragit E) in a substance with a melting point of 40-120 °C, a sugar alcohol (e.g. sorbitol) and a basic oxide (particularly MgO).

WO 98/46239 discloses a delayed-release pharmaceutical formulation containing an erythromycin derivative and a hydrophilic water-soluble polymer, which in oral use has an improved taste profile and fewer gastrointestinal side effects in comparison with the common form. The preparation technology includes, *inter alia*, wet granulation, drying, sieving and milling processes.

Thus, numerous publications exist in the patent and other literature in that field disclosing the composition and preparation of various pharmaceutical formulations with clarithromycin. However, we have not found any literature source disclosing such a simple process for the preparation of a clarithromycin suspension having such a

simple composition, a good smell and taste as well as a possibility of upgrading for diabetics. Additionally, it also enables the controlling of the rate and the site of the release of the active component.

Technical Solution

The aim of the present invention is a new oral pharmaceutical formulation with clarithromycin or derivatives thereof. Surprisingly, the bitter taste of clarithromycin has been very successfully masked by coating clarithromycin, which may be present alone or in a homogeneuos mixture with conventional adjuvants, with a lipid film-forming substance having a low melting point (below 100 °C). The granulate was prepared in the melt in a mixer-granulator, thus in one step and in one vessel without the use of any solvents. From the granulate various conventional final pharmaceutical formulations such as suspensions in concentrations of 125 mg/5 ml and 250 mg/5 ml, tablets or capsules can be prepared.

The base for coating can be clarithromycin itself or its mixture with excipients such as lactose, calcium carbonate, sodium hydrogen phosphate, NaCl, citric acid, PEG or stomach-insoluble polymers such as Eudragit L or S (1:1 or 1:2 copolymer of methacrylic acid and MMA), microcrystalline cellulose etc. The weight ratio between clarithromycin and these excipients amounts from 5:1 to 1:1.2

As the lipid film-forming substance almost insoluble in water there can be used a higher fatty alcohol, preferably stearyl, cetostearyl or cetyl alcohol or a suitable acid such as stearic acid or a physical mixture or an ester of several such components e.g. stearyl stearate. The weight ratio between clarithromycin and these excipients amounts from 2:1 to 1:2.

The melt granulation is performed in such a way that a mixture of clarithromycin (possibly with addition of adjuvants) and of the lipid for coating is heated in a granulator under mixing to the melting point of the lipid component and then the

obtained granulate is slowly cooled. For the final preparation of the granulate for suspensions there are also added viscosity enhancers and stabilizers such as xanthan gum, guar gum, silica gel, magnesium aluminium silicate etc. For a better taste, smell and appearance, sugar or sweetening agents such as aspartame, sodium saccharinate or erythritol, caramel, vanilla or fruit flavours and colouring agents can also be added. However, all the cited additives for the preparation of suspensions cannot cover the bitterness of clarithromycin by themselves.

The pharmaceutical formulation of the present invention can be improved by using polyols instead of sugar, which makes it also suitable for diabetics. For this purpose e.g. xylitol and mannitol and their combinations with maltitol, maltol and sorbitol can be used. Thus, the present pharmaceutical formulation represents the only oral suspension with clarithromycin, which is not based on sugar (saccharose).

Fatty alcohols such as stearyl alcohol possess, in proportion to their concentration, a delaying effect on the release of the active component from the pharmaceutical formulation. This property can be used for controlling the clarithromycin release rate and an oral suspension with delayed action can be prepared.

Additionally or optionally, by applying a gastroresistant layer onto the granulate base from the melt, the site of clarithromycin release in the alimentary tract can be affected. Polymers forming a gastroresistant coating such as shellac, cellulose acetate phthalate, HPMC phthalate, ethylcellulose latex, polymethacrylates etc. can be used therefor.

The present invention is illustrated but in no way limited by the following Examples:

Example 1

In a mixer-granulator 2 kg of clarithromycin and 2 kg of stearyl alcohol were homogeneously mixed. During mixing it was heated to the melting point and a

chopper was switched on. Then it was cooled under constant mixing. Spherical granules/pellets were formed. Dry additives were added thereto.

Dry additives per vial or per 5.00 g of clarithromycin-stearyl granulate (pellets):

Na_2HPO_4	1.000 g
NaCl	1.000 g
aspartame	0.100 g
aerosil	0.400 g
vanilla flavour	0.070 g
ammonium glycirhizinate	0.140 g
xylitol	60.690 g
methyl hydroxybenzoate	0.260 g
titanium dioxide	0.050 g
quinoline yellow colouring agent	0.010 g

total dry matter per vial	69.000 g
water added	55.000 g
suspension volume obtained	100.000 ml
suspension content	125 mg clarithromycin /5 ml

Example 2

The process was identical to that of Example 1, only that 1.25 kg of clarithromycin, 1.25 kg of stearic acid and 1.5 kg of NaH_2PO_4 were homogeneously mixed.

Dry additives per vial or per 7.2 g of clarithromycin-coated granulate (pellets):

NaCl	1.000 g
aspartame	0.100 g
aerosil	0.400 g

caramel flavour	0.070 g
erytritol	0.140 g
maltitol	60.690 g
methyl hydroxybenzoate	0.260 g
titanium dioxide	0.050 g
quinoline yellow colouring agent	0.010 g
citric acid	0.010 g

Example 3

The preparation of the granulate was identical to that of Examples 1 or 2.
Additionally, a gastroresistant coating was applied; for 200 mg of pellet cores the following dispersion was prepared:

HPMC phthalate 55	48.612 mg
dibutyl sebacate	0.893 mg
talc	0.495 mg
ethanol	332.143 mg
acetone	332.143 mg

If a gastroresistant coating was applied, the amount of the sweetening agent was reduced for 50 mg; otherwise the preparation of the final suspension was identical to the one of Example 1.

Example 4

The preparation of the granulate was identical to the one of Examples 1 or 2.
Additionally, a gastroresistant coating was applied; for 500 mg of pellet cores the following water dispersion was prepared:

Eudragit L 30 D-55	48.612 mg
triethyl citrate	0.893 mg
talc	0.495 mg
water	332.143 mg

The preparation of the water dispersion: triethyl citrate, talc and the antifoaming agent were dispersed in water and homogenized. Immediately before use, it was added under stirring into the Eudragit dispersion and filtered.

Claims

1. Pharmaceutical formulation in the form of a granulate for oral use, characterized in that it contains clarithromycin or its derivatives coated with a lipid substance.

2. Pharmaceutical formulation according to claim 1, characterized in that clarithromycin or its derivative is admixed with other pharmaceutically acceptable additives.

3. Pharmaceutical formulation according to claim 2, characterized in that the pharmaceutically acceptable additive is a polymer insoluble in stomach.

4. Pharmaceutical formulation according to claim 3, characterized in that the polymer insoluble in stomach is a copolymer of methacrylic acid and methyl methacrylate.

5. Pharmaceutical formulation according to claim 1, characterized in that the lipid substance is a higher fatty alcohol or a suitable acid or a mixture thereof.

6. Pharmaceutical formulation according to claim 1, characterized in that it is, by the addition of other pharmaceutically acceptable substances, prepared in the form of tablets or capsules.

7. Pharmaceutical formulation according to claim 1, characterized in that it is, by the addition of other pharmaceutically acceptable substances, prepared in the form of a suspension.

8. Pharmaceutical formulation according to claim 7, characterized in that it is prepared without sugar (saccharose).

9. Pharmaceutical formulation according to claim 7, characterized in that polyols are added as sweetening agents.

10. Pharmaceutical formulation according to any of claims 1 to 6, characterized in that, additionally, a gastroresistant coating is applied.

11. A process for the preparation of a pharmaceutical formulation according to claim 1, characterized in that it comprises a homogeneous mixing of a coating mixture, melt granulation, cooling and an addition of other excipients for the formation of a granulate.

12. A process for the preparation of a pharmaceutical formulation according to claim 11, characterized in that it is completed by applying a gastroresistant coating.

13. Pharmaceutical formulation in granulate form for oral use, characterized in that it is prepared according to the process of claim 11.

14. Pharmaceutical formulation according to claim 1 useful for the treatment and prophylaxis of bacterial infections.

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(71) Applicant *(for all designated States except US)*: **LEK, TOVARNA FARMACEVTSKIH IN KEMIČNIH IZDELKOV, D.D.** [SI/SI]; Verovškova 57, 1526 Ljubljana (SI).

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(57) Abstract: The present invention discloses a simple one-step process of coating by means of melt granulation for effective masking of bitterness, and a new, patient-friendly oral pharmaceutical formulation suitable also for diabetics, which at the same time also enables variations in the rate and site of the release of the active component.

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 17667 A (TAISHO PHARMACEUTICAL CO., LTD.) 16 September 1993 (1993-09-16) the whole document & US 5 707 646 A 13 January 1998 (1998-01-13) cited in the application	1,2,5-9, 14
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Y	page 1, line 5 - line 11 page 9, line 14 -page 10, line 25 page 16, line 1 -page 17, line 8 page 19; examples 3,4	1,6,11, 12

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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